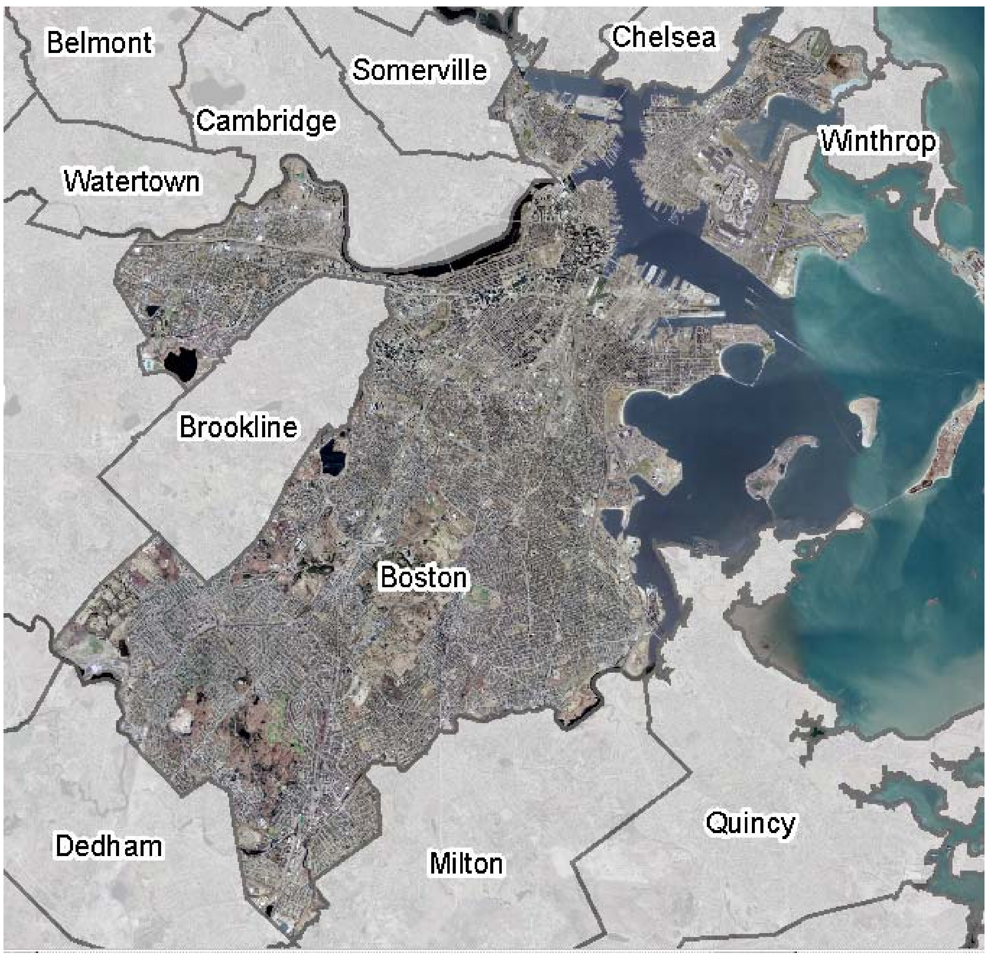
Final Report on
The Incidence and Prevalence of Systemic Lupus Erythematosus (SLE) in Boston and Environmental Factors



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BACKGROUND / INTRODUCTION

In response to a line item directive in the Massachusetts Acts of 2001, the Massachusetts Department of Public Health (MDPH) designed and implemented a surveillance system to better understand the prevalence and patterns of individuals diagnosed with systemic lupus erythematosus (SLE). The surveillance system (or "registry") was targeted on the City of Boston, given that funding provided was insufficient to carry out a statewide initiative. To supplement state resources and to better understand the potential relationship between SLE and environmental factors, MDPH sought and received federal funding from the U.S. Centers for Disease Control and Prevention (CDC).

In 2003, Massachusetts became one of seven states and large cities receiving funding from the CDC, to implement demonstration projects aimed at linking environmental data with health outcome data. Massachusetts was the only recipient that proposed establishing a population-based surveillance system for SLE. The linkage of SLE data with environmental data is referred to as the SLE tracking project.

Prior to this effort, incidence and prevalence rates for SLE specific to Massachusetts and its communities were not known. Studies in other states and countries have indicated a wide variation in rates and may not be comparable due to inconsistencies in case definitions and case ascertainment techniques. As mentioned, the SLE tracking project aimed to establish a surveillance system for the entire City of Boston. Through the development and implementation of this pilot surveillance, information was also obtained to help determine the feasibility of establishing a system for statewide lupus surveillance.

Lupus is a serious chronic autoimmune disease of complex etiology that affects multiple organ systems, including joints, skin, kidneys, heart, lungs, blood cells, blood vessels and/or the brain. Patients may experience unexplained fever, skin sensitivity to the sun, other skin rashes, swollen glands, kidney problems, extreme fatigue, neurologic symptoms, and/or low blood counts. Manifestations are highly variable, and may change over time as the immune system attacks different systems.

Lupus occurs primarily in women (*Kaslow and Masi, 1978*). Women of African American and Asian descent are at greater risk of having SLE and have the highest mortality. In 2002, the CDC presented a report that analyzed lupus deaths and found that age, sex, and race specific disparities exist in SLE mortality rates and that mortality rates increased by approximately 70% during the period 1979-1998 among African American women aged 45-64 years (*Sacks and Helmick, 2002*).

Lupus is a disorder with complex causes. While the exact etiology is not known, genetics is thought to play a role in the occurrence of the disease (*NIH, 1997*). The scientific literature suggests that environmental factors may play a role (*Mayes, 1999; Powell et al., 1999*). Several studies have shown that occupational exposure to chemical solvents is a risk factor in lupus and other closely related disorders. In a case-control study in Michigan and Ohio, Lacey et al. (1999)

found that women with occupational exposure to paint thinners or removers (an interchangeable term used for many products all of which are of petroleum distillates) had significantly higher levels of connective tissue disorders (lupus is an arthritis-related disease that also impacts connective tissue). Increased risk of lupus has been seen in studies examining occupational exposure to silica dust as well (*Conrad et al., 1996; Sanchez-Roman, 1993*), and there is also evidence of increased risk among individuals at risk of exposure to chlorinated solvents (*Yoshida and Gershwin, 1993*).

Many of the contaminants evaluated in previous studies (e.g., petroleum distillates) are ubiquitous in the environment and can be found in hazardous waste and other air pollution sources. There is currently no uniform surveillance system in place to examine potential patterns between various types of pollutants and incidence patterns of lupus. This report describes methods to link lupus surveillance and environmental data to evaluate possible patterns that may prompt further public health research into the environmental risk factors for lupus.

METHODOLOGY

In order to estimate the incidence and prevalence of SLE and to demonstrate the feasibility of extending standardized surveillance of SLE to other geographic areas of the Commonwealth, this initial effort was focused on the City of Boston. The primary method of case finding was in- and out-patient medical records of eleven hospitals representing the catchment area for individuals diagnosed with lupus and residing in Boston. The eleven hospitals included:

- Beth Israel Hospital
- Boston Children's Hospital
- Boston Medical Center
- Brigham and Women's Hospital
- Caritas Saint Elizabeth's Medical Center
- Faulkner Hospital
- Massachusetts General Hospital
- Milton Hospital
- Mount Auburn Hospital
- New England Baptist Hospital
- Tufts-New England Medical Center

A review of clinical lists from Boston Neighborhood Health Centers and a survey of private rheumatologists statewide was also conducted as case ascertainment validation for the primary surveillance method.

Case Ascertainment

1. Data Sources

Cases

As mentioned, the primary source of SLE cases among Boston residents were hospital databases of 11 participating hospitals identified by a MDPH scientific advisory committee as the most likely to serve Boston lupus patients. The advisory committee for this effort was composed of area rheumatologists, medical records personnel, and others. Boston residents with a diagnosis coded for SLE (ICD-9 710.0) or lupus erythematosus (LE) (ICD-9 695.4) as primary or secondary diagnoses were identified retrospectively by participating hospitals for subsequent review of medical records by MDPH nurse abstractors.

Although ICD9 code 695.4 is defined as “not systemic” and should therefore exclude SLE, this code was included since its designation as LE may result in miscoding (the potential for this miscoding was confirmed by MDPH staff in a small sample at a large participating hospital).

Target Population

As described earlier, the target population for this surveillance effort was residents of the City of Boston. The source of population data for rate calculations was the 2000 Census. The definitions of Boston neighborhoods by census tracts and used for this report were established by the Boston Redevelopment Authority (BRA) (April 2001). Although, it was of interest to determine the race of SLE cases and to report on the incidence and prevalence by racial category, it was found that hospital data often reflected race as “White,” “Black,” “Hispanic,” “Asian,” etc, while the U.S. Census now characterizes race differently (e.g., “non-Hispanic White,” “Hispanic

White," etc). Thus, it was not possible to determine the incidence and prevalence of SLE cases by race.

2. Case Definition

The criteria below served as the case definition for this surveillance effort:

a. At least one in- or out-patient medical visit during the surveillance year October 1, 2003 through September 30, 2004, with a primary or secondary diagnosis coded as ICD-9 710.0 or 695.4 in the hospital database of at least one of the 11 participating hospitals.

b. Boston residence based upon home Zip Code stated in the medical record at the time of case ascertainment.

c. Any diagnosis of SLE (definite, probable or possible) abstracted from medical record review. Fulfillment of this criterion required written notation in a medical record indicating a diagnosis of possible, probable or definite SLE, which was not subsequently superseded by a statement indicating "no SLE" by a physician with at least equivalent expertise. Only reference to the disease by name or by standard abbreviations was accepted. Laboratory results or use of terminology such as "connective tissue disease," or "autoimmune disease" were insufficient.

3. Data Collection

In November 2004, a letter of request was mailed from the Associate Commissioner of the Center for Environmental Health (CEH)/Massachusetts Department of Public Health

(MDPH), to the director of the medical records unit for each of the 11 participating hospitals. The letter included a summary of and citation for the Department's authority to conduct the surveillance, and itemization of the selection criteria and fields required for their report. Each letter was followed by several phone calls and sometimes site visits with hospital personnel from medical records. Occasionally, there was communication with hospital IT staff for clarification of the query and facilitation of abstraction arrangements.

Each participating hospital generated a "Hospital List" by querying its hospital database for the previously stated criteria with regard to date of encounter, primary and secondary diagnosis ICD-9 codes, and zip code of residence. This "Hospital List" was used by the medical records department and sometimes the rheumatology clinic at each hospital to pull medical records for review by MDPH abstractors. Sometimes clinic records had to be reviewed at a location other than hospitalization records. The only clinic records reviewed were from rheumatology clinics. Trained nurse abstractors used an abstraction form developed by MDPH specifically for this surveillance project.

Assessment of Case Ascertainment Completeness

Two additional case identification approaches were taken in order to evaluate whether cases might be missed by the case ascertainment method described above that is limited to hospitals. These approaches included the Neighborhood Health Center (NHC) Survey and Statewide Rheumatologist Survey. While both approaches were intended to determine if cases might be missed, the Rheumatologist Survey also attempted to evaluate a methodology for ascertaining cases statewide that might not require medical record abstraction.

1. Neighborhood Health Center (NHC) Survey

A similar letter of request was sent to each of the 27 NHCs serving Boston residents. NHCs supplied CEH with a list of Boston patients who had had a medical visit to their center between Oct 1, 2003 and Sept 30, 2004, that was associated with an ICD 9 code of 710.0 or 695.4. Zip code and identifiers similar to Part I of the hospital surveillance were obtained for each patient. As in the hospital surveillance, dates of diagnoses and level of certainty of SLE diagnosis were not available through the databases. NHC medical record review was not performed.

2. Statewide Rheumatologist Survey

A letter of request that included a short reporting form was sent to each of 241 physicians registered with the Massachusetts Board of Registration in Medicine as specializing in rheumatology. Information was requested for patients with a diagnosis of probable or definite SLE made between Jan 1, 2000 and before December 31, 2004. Data requested included date of diagnosis, name of patient, address, date of birth, date of death (if applicable), race, gender, and last 4 digits of each individual's social security number. Reminder letters with additional forms were mailed to those that had not responded within three weeks. The primary purpose of this survey was to explore the methodology for a statewide registry, and importantly to identify missed cases among Boston residents.

Case Geocoding

A geographic information system (GIS) database containing addresses and spatial locations of all tax-assessed properties in Boston was obtained from the Boston Redevelopment Authority (BRA). To facilitate matching between the databases, addresses in the participant address file were standardized with the United States Postal Service database (Datatech Smartsoft 2006). Wherever possible, study participant addresses were matched to taxed property locations (Environmental Systems Research Institute 2005). Using a GIS street centerline database, the majority of addresses that did not have a corresponding address match in the tax data were able to be geocoded (Geographic Data Technology 2006). In some instances addresses were validated using online mapping tools and digitized, or manually mapped to their corresponding locations.

Estimation of Rates

Incidence (i.e., the number of new cases diagnosed over a specific time of interest) and prevalence (i.e., number of new and existing cases at the time of data collection) rates were estimated using 2000 Census data. In both cases, rates were presented as the number of cases per 100,000 population. Rates were not adjusted for age, gender, or race/ethnicity. Prevalence rates were estimated only for Boston as a whole and represent the number of SLE cases among Boston residents who had an in- or out-patient hospital visit between October 1, 2003 and September 30, 2004. The incidence of SLE represents the average annual number of new cases of lupus diagnosed among Boston residents for two time periods; October 1, 2003-September 30, 2004 (the period cases visited a hospital) and January 1, 1999-September 30, 2004 (the maximum period clinical information was collected to identify new cases). Average annual incidence rates were estimated for Boston as a whole and for each Boston neighborhood. Only rates based on at least 5 cases could be shown, however, in order to protect privacy (i.e., very small numbers of cases could lead to the identification of individuals because of the rarity of the disease).

Standardized Incidence Ratios (SIRs) were calculated to determine if the rate of definite and probable cases of SLE was elevated in specific Boston neighborhoods. SIRs generally use a large population, such as the state population, as the standard population. Because SLE rates are unknown for Massachusetts as a whole, the Boston population and the rate of SLE incidence, as determined by this surveillance effort, was used as the standard population. Specifically, an SIR is the ratio of the observed number of new lupus cases in an area (in this case, a specific Boston neighborhood) to the expected number based on a larger more stable population (in this case, Boston) multiplied by 100. An SIR of 100 indicates that the number of new lupus cases observed in the population being evaluated is equal to the number of cases expected in the comparison or "normal" population (in this project it is the city of Boston as a whole). An SIR greater than 100 indicates that the incidence of lupus is greater than expected. An SIR less than 100 indicates that fewer cases were observed than were expected. Accordingly, an SIR of 150 is interpreted as 50% more lupus cases than the expected number.

Caution should be exercised, however, when interpreting an SIR. The interpretation of an SIR depends on both the size and statistical stability of the SIR. Two SIRs can have the same size but not the same stability. To help interpret or measure the stability of an SIR, the statistical significance of each SIR is assessed by calculating a 95% confidence interval (CI) to determine if the observed number of cases is "statistically different" from the expected number or if the difference may be due solely to chance. If a confidence interval does not include 100 and the interval is greater than 100 (e.g., 105-130), there is a statistically significant excess in the number of cases. Similarly, if the interval does not include 100 and the interval is below 100 (e.g., 45-96), the number of lupus cases is statistically significantly lower than expected. If the interval includes 100, the true SIR may be 100 and the observed number of cases may not be different from the number expected.

Environmental Data Collection

The primary source of environmental data for this surveillance project was derived from environmental databases maintained by the Massachusetts Department of Environmental Protection (MDEP). These databases contain information that allowed MDPH to geocode sites or areas of environmental contamination, as well as assign specific criteria to each site (e.g., determining if a site contains pollutants of interest).

Under Massachusetts General Law, Chapter 21e, MDEP regulates all hazardous waste sites within the Commonwealth of Massachusetts. These are characterized by one or more releases of oil or other hazardous materials. Releases can result from a variety of sources, including oil trucks, underground storage tanks and aboveground storage drums. Releases vary widely with respect to materials involved, the amount of materials released and the geographic extent of contamination. State law mandates the reporting of all spills involving potentially hazardous waste to MDEP. Information on hazardous material and oil releases, including assessment and remedial response measures, is available from 1986 to present. However, the environmental data available in these databases are, for the most part, limited to information collected during the initial stages of the identification of the site and the characterization of exposure. Information included in this electronic database includes:

- Address and Location of a Site
- Date(s) of Spill(s)
- Source of Spill
- Chemical(s) Spilled
- Amount(s) Spilled
- Cleanup Actions
- Phase of Cleanup
- Duration of Cleanup
- Risk of Human Exposure
- Current Site Status

In addition, these sites were further queried by type of site and chemical spilled, as well as location. Figure 1 (page 37) depicts a flow chart showing the number of hazardous waste sites in Boston by category. The contaminants present and the potential for exposure are not always clear from the database, however. Therefore, in addition to evaluating the presence of 21e sites as a whole, categories of sites were selected for linkage that would include those believed to offer the greatest potential for exposure and/or relevance to lupus. The boxes in bold on Figure 1 (page 37) represent those selected for linkage with the lupus surveillance data. "Total Sites Mapped" was selected so that analyses could be done looking at all sites. "All Tier Classified Sites" were analyzed because these are sites that have been initially evaluated but required further assessment or remediation after a year or more.[1] They are considered to pose the greatest threat to the environment. "Tier Classified Sites with Lupus Suspect Chemical Categories" are a subset of Tier classified sites. These sites included those with a file notation that chemicals at the site include one or more of the chemicals suggested in the literature as potentially associated with SLE. The types of chemicals evaluated in the literature primarily include petroleum distillates, such as gasoline. Others are various types of oils, chlorinated solvents, and polycyclic aromatic hydrocarbons (PAHs). Because of the focus on some specific chemicals, our analyses also evaluated the categories of "Hazardous Waste Sites with Gasoline Contaminants" and "Hazardous Waste Sites with Polycyclic Aromatic Hydrocarbon Contaminants." Figures 2 and 3 illustrate the geographic distribution of some selected sites.

[1] MDEP has different levels of the classification to reflect different priority levels for site characterization and remediation. However, scoring to determine levels for tier classification was not uniformly carried out until 1993; hence, analyses were conducted using all the classified sites as a single category.

Environmental Data Analysis

A geographic information system was developed for linkage between the lupus case dataset and the MDEP 21e hazardous waste site data set. Specifically, analyses were conducted that assessed whether the incidence of lupus was associated with the density of the categories of hazardous waste sites described previously.

1. 21e Data Mapping

A database of historical 21e records was obtained from MDEP (Massachusetts Department of Environmental Protection 2003). Unlike the lupus case residential addresses, the collection of location information in the 21e database is not standardized. All addresses and location information in the database were reviewed manually and corrections and standardizations were made wherever possible. Mapping was achieved through a combination of exact parcel matching, street address geocoding, and on-screen digitizing using the aforementioned reference data sources. In cases where the location information for 21e records was incomplete or non-specific, attempts were made to estimate the mapped point placement using historical resources and subjective judgment. It should be noted that 21e sites vary with respect to overall size; thus point mapping is an approximate representation of the actual extent of any potential environmental release or contamination.

2. Spatial Density Estimation of 21e Sites

For the purposes of this analysis, boundaries and total area for each of the 17 Boston neighborhoods were defined by aggregating 2000 Census tract areas (Boston Redevelopment Authority 2001). Once the 21e sites were mapped, each point was assigned to one of the 17 Boston neighborhoods using a GIS overlay. Total counts were divided by total area to compute spatial densities for each 21e category for each neighborhood. Chi Square statistics and Odds Ratios were estimated to determine statistical significance at the 95% confidence level. Because some sites are believed to only have the potential for releasing contaminants after the cases in our analyses were diagnosed (i.e., in 1999 or later), the sites included in our analyses were restricted to those where the suspected release was prior to 1999.

RESULTS

Case Ascertainment and Eligibility Results

There were 927 patients who were identified by the hospitals (all hospitals participated) as being Boston residents and having an in- or out-patient visit between October 1, 2003 and September 30, 2004, coded as lupus. The records of each patient were reviewed and abstracted to determine eligibility, since having a hospital visit coded as lupus does not mean that the patient actually had a diagnosis of lupus. Each of the 927 abstractions, with its unique ID number, was entered by MDPH data entry personnel into a text file that was then imported to an Access database.

Figure 4 (page 40) shows the results of determining case eligibility for the hospital surveillance. Duplicate cases were first identified using a combination of name, date of birth, and last four digits of the social security number. There were 831 unique individual patients identified. Most of the matches were the result of a patient being seen at more than one facility, and a few were due to more than one medical record number at the same facility, or inadvertent duplication of abstraction by the nurse abstractors. For individuals with multiple abstractions entered, a new consolidated record in the database was created, selecting the highest level of expertise among the entries for diagnostic certainty of SLE, and among those, the most recent level of certainty. The earliest date of diagnosis among the multiple entries was selected for entry to the consolidated record. The address selected was the earliest for which we were confident of the date. The final analyses were based on the consolidated records of individuals with multiple entries, and the single records of those with only one abstraction.

The flowchart in Figure 4 (page 40) provides general reasons for ineligibility. Of the 831 patients, 30 were determined to have residential addresses that were either outside Boston (n=24) or not able to be mapped (n=6). Among the 801 patients remaining, 591 were found to have a notation of definite, probable or possible SLE in a reviewed medical record. Of the 210 excluded on the basis of diagnosis, 51 were indeterminate for SLE diagnosis by our criteria and 159 were considered not to have SLE.

Some analyses were restricted to cases whose earliest date of diagnosis (definite, probable, or possible) was 1999 or later. There were 333 pre-1999 diagnoses and 38 for which a date of diagnosis could not be determined. From the 220 eligible by residence and date, 178 had a definite or probable diagnosis of SLE and were used in comparisons of Boston Neighborhoods and linkage to environmental data.

Among the 220 cases diagnosed as definite, probable, or possible SLE cases since 1999, 185 (84.1%) had a rheumatologist's note in the medical record indicative of the level of certainty. The abstractors indicated that at least 156 (71%) of the 220 diagnoses were made in outpatient facilities, 23 (10%) during hospitalizations, and 41 (19%) were left as uncertain or blank.

Case Demographics and SLE Rates

1. Distribution by Gender and Age

Table 1 (page 44) presents the total number of SLE cases broken down by gender for different case definitions. The most certain cases (i.e., definite or probable) for more recent diagnoses (i.e., 1999 or later) had a female/male ratio of 9:1, similar to that described in the literature.

Figure 5 (page 41) displays the age distribution for different categories of cases. As expected, except for a small number of cases diagnosed in the newborn period (neonatal lupus), case diagnoses began in the second decade of life, with the largest number of recently diagnosed cases (diagnosis 1999 or later) occurring between 20-49 years of age, similar to the typical age at onset as described in the literature. The case definition group that included all cases without regard to date of diagnosis demonstrated a relatively older age distribution than the 2 groups that included only recent cases. This is due to the accumulation of surviving cases that were diagnosed a long time ago at a younger age.

2. Estimates of Prevalence

Table 2 (page 44) provides the case counts and prevalence rates for Boston as a whole, using different categories of cases. For all three categories, the numbers reflect only those SLE patients who came for medical encounters recorded in hospital in- and/or out-patient databases of any of the 11 participating facilities during our surveillance year, October 1, 2003 to September 30, 2004.

The overall incidence rate for Boston among cases with a definite, probable, and possible diagnosis with any year of diagnosis was 100.3 per 100,000 persons during our surveillance year. The prevalence of definite and probable diagnoses alone are those cases most comparable to other estimates of prevalence in the scientific literature. It was observed from analyses shown in Table 1 (page 44) that the proportion of cases that were definite or probable lupus cases was about 80 percent. Applying this figure to the number of cases identified for all years of diagnosis, it is estimated that the prevalence of definite and probable SLE was 80.3 per 100,000 population. Table 3 (page 45) is a summary table of the Boston prevalence estimates by gender and case definition for all years of diagnoses.

3. Estimates of Incidence

During the period October 1, 2003 - September 30, 2004, the annual incidence rate for new definite, probable or possible SLE cases in Boston is 9.7 per 100,000. Excluding cases with only a "possible" diagnosis results in an incidence rate of 6.3 per 100,000 (Table 4 – page 45).

4. Boston Neighborhood Comparisons

Table 5 (page 46) presents the case count, population size, and calculated average annual incidence rate of cases for each of the 17 Boston Neighborhoods and Boston as a whole for diagnoses from 1999 through September 30, 2004. The neighborhoods that have the highest rates are Roxbury, Mattapan, and Hyde Park, with Roxbury having a statistically significantly higher incidence rate than Boston as a whole.

Table 6 (page 47) presents the Standardized Incidence Ratio (SIR) for each of the 13 Boston Neighborhoods that had 5 or more cases with a definite or probable diagnosis since 1999. These results again show that the neighborhood of Roxbury demonstrated a statistically significant elevation in the occurrence of SLE. The neighborhood of Allston/Brighton had a statistically significantly lower rate of SLE.

Neighborhood Health Survey (NHC Survey): Figure 6 (page 42) illustrates that of the 137 patients reported by the NHCs, 53 had not been captured by the hospital queries that resulted in identifying 831 individuals who met the criteria for inclusion in this surveillance effort focused on Boston. It isn't known if all 53 cases had definite or probable SLE because a detailed clinical medical record review could not be done. From the experience of identifying and reviewing hospital records, only about 46 percent of the records originally identified by hospitals as records of lupus patients were determined to be definite or probable SLE. Therefore, if this experience holds true for the NHCs, then about 24 of the 53 cases may have been definite or probable SLE cases. The NHC survey then suggests that about 24 cases may have been missed by not including NHC data.

Statewide Rheumatologist (Rh) Survey: The Statewide Rh Surveillance met with much resistance reportedly due to the retrospective nature of the surveillance. Out of the 241 rheumatologists mailed requests, written responses were received from 98, ten of whom suggested that they didn't submit a count because they were not currently in Rheumatology practice, or had no access to a database. Thirty-two rheumatologists reported having no patients with an SLE diagnosis. The remaining 56 responding rheumatologists resulted in a total of 328 SLE patients, with a range of 1-67 patients reported per physician.

Only 8 rheumatologists reported having SLE patients residing in Boston, with 9 Boston SLE patients reported in total. Two had been identified by our hospital surveillance as well. Of the seven that were not captured by the hospital surveillance, 3 were reported by rheumatologists with practices in Boston, and 4 from practices in other parts of Massachusetts. While these data are incomplete, they suggest that at least some cases may be missed if surveillance only includes prevalent cases identified through hospital records. Other rheumatologists with patients having

Boston residences either did not respond or submitted “0” for the number of SLE patients.

5. Linkage of SLE prevalence and density of hazardous waste sites

The environmental linkage analyses were performed using only the cases with a definite or probable diagnosis and having a diagnosis since 1999 (n=178).

As mentioned earlier, Figure 1 (page 37) shows the number of 21e hazardous waste sites from MDEP records for the City of Boston by type of site. Of the 3,252 sites on record, 1,706 sites were known to exist prior to 1999 and were geocoded and mapped. There were 1,521 of these sites for which there was some chemical information. Five hundred nine sites were tier classified sites, with 369 of those having chemicals that some studies have suggested might be associated with SLE (i.e., chlorinated solvents, oil, gasoline, PAHs and mercury). The 21e site categories that were used for the linkage analyses are represented with bold lines and letters in the flowchart (Figure 1 – page 37) and shown below:

- All mapped 21e sites (n=1,706)
- All tier classified sites (n=509)
- All tier classified sites with information indicating chemicals suspected to be associated with lupus (n=369)
- All mapped sites with gasoline contaminants (n=183)
- All mapped sites with PAH contaminants (n=132)

Table 7 (page 48) displays for each neighborhood the number and classification of 21e sites in Boston neighborhoods. Densities of 21e sites within each neighborhood were calculated from the counts of a selected category of 21e site within that neighborhood, divided by the area (sq mi) of the neighborhood, as described under Methodology.

To further explain the possible relationship between lupus prevalence of cases diagnosed in 1999 or later and the density of 21e sites for each of the contaminant categories evaluated, the density data was dichotomized. For these analyses, each neighborhood was assigned a “higher” or “lower” density level for each category of 21e sites. The mid-range of the density values for each neighborhood was selected as the distinction between higher and lower density. Neighborhoods with a density value above the mid-range for that 21e category would be considered a higher density neighborhood. Similarly, those with values below the mid-range would be considered lower density neighborhoods.

Tables 8a-8e display the cases, population and incidence for higher and lower site density neighborhoods, and the corresponding odds ratio, chi-square and p-value created for each of the selected 21e classifications. Table 8a (page 49), demonstrates that for “All 21e Sites Combined,” there was no association (i.e., a greater percentage of cases present in the Neighborhoods with higher 21e site density was not observed). However, when those sites considered “tier classified” were evaluated, a statistically significant association between higher lupus incidence and higher density of tier classified sites had been observed (Table 8b – page 49). Average annual incidence in the higher density neighborhoods was 6.4 per 100,000 compared with 4.4 in the lower density neighborhoods. Similar findings were seen when only those tier classified sites with "lupus suspect contaminants" were examined (Table 8c – page 50); prevalence was again 6.4 per 100,000 in the higher density areas and 4.4 in the lower density areas.

Table 8d (page 50) shows the results for the sites with gasoline contaminants. Statistically significant findings were again seen here. Sites with PAHs also showed a statistically significant association between prevalence and site density (Table 8e – page 51).

DISCUSSION

The estimated crude prevalence rate of 100.3 per 100,000 population (All Races) includes the less definitive "possible" cases, which are usually not included by other researchers in estimates of prevalence. Only medical records for cases diagnosed since 1999 could be reviewed to determine if the case was a definite or probable diagnosis of lupus, therefore the prevalence of definite or probable cases, regardless of date of diagnosis, had to be estimated based upon the data collected since 1999. Cases diagnosed in 1999 or later suggested that about 80 percent of cases had a diagnosis of definite and/or probable SLE. Thus, for all SLE cases ascertained in this surveillance effort, the estimated prevalence of definite or probable lupus was 80.3 per 100,000 population. Both of these rates seem to be in the range of other reports of prevalence in the US. That range is 5.8 to 130 per 100,000 population. Some of the variation in rates in the US may be due to differences in data sources, case definitions, and methods of data collection (e.g., patient reporting with a variety of questionnaires; rheumatology practices; hospital admissions; varying utilization of American College of Rheumatology (ACR) criteria), as well as differences in size and racial distribution of the populations under consideration. For example, National Health and Nutrition Examination Survey (NHANES) III U.S. estimates the prevalence of lupus as 241 per 100,000 population and 53.6 per 100,000 population for self-reported physician diagnosis of SLE and self-reported physician diagnosis of SLE with treatment, respectively, among household adults age greater than or equal to 17 years. While the former may be an overestimation of SLE prevalence, the latter prevalence is an underestimation, since not only are undiagnosed cases lacking, but also not included are those cases that did not have a current prescription of anti-malarials, corticosteroids, or other immunosuppressive drugs. When the Boston population is restricted to those greater than or equal to 17 years of age as in NHANES III, the prevalence of “All Races” in Boston (definite, probable, and possible diagnoses for any year of diagnosis) becomes 120.1 per 100,000 population, still between the national survey’s two rates. The population that the NHANES III sampled was much smaller than this MDPH effort (about 20,000 participants compared to a study population of about 590,000) and likely had a different racial distribution, including a larger proportion of the lowest risk racial group, non-Hispanic White. The age distribution presented in this report along with female/male ratios, also all seemed consistent with the scientific literature.

An interesting incidental observation was made in the process of excluding cases <17 years of age for the NHANES comparison of rates. Of the 12 cases <17 years, half were male.

This is in sharp contrast to the ratio of more than 9 to 1 seen among our cases for all ages combined, and frequently described in the literature for combined ages. Although more of these may have been only "possible" cases, the possibility that the female/male ratio is lower among pediatric SLE patients than among adults warrants further attention. If this is a consistent finding, a different etiologic mechanism in pediatric SLE might be an area for further research.

As mentioned, due to the difficulties in obtaining comparable race and ethnicity from hospitals of the cases identified and BRA data, prevalence could only be estimated for all races combined. This difficulty might be avoided in future data collection activities if surveillance was conducted as new cases are identified (i.e., prospectively) rather than attempting to identify cases diagnosed a number of years ago (i.e., retrospectively), as was carried out in this project. In future research, it would be important to expand the surveillance methodology so that reliable information on race could be obtained, since prevalence estimates compiled from the literature by Bae et al (1998) ranged from 17.9 to 283 per 100,000 for African Americans, which are 4 – 10 times higher than estimates for Caucasians. Furthermore, non-Whites have a higher mortality from lupus suggesting disparities in access to health care or true differences in severity of disease among African-Americans. Race-specific prevalence data would give greater focus on these discrepancies in disease occurrence. Beginning in July of 2007, Boston hospitals, as well as other Massachusetts hospitals, will begin recording the race and ethnicity of patients using a standard format that will be consistent with that used by the MDPH and U.S. Census (and the BRA). This change will greatly facilitate the estimation of race-specific prevalence.

Neighborhood-specific rate information was obtainable only for the period 1999 through September 30, 2004. Prevalence cases (i.e., new and existing cases) for this period represented only about one-third of all Boston cases. Therefore, prevalence rates by neighborhood were not estimated. Instead, incidence or the number of new cases diagnosed since 1999 was estimated by neighborhood. While precise estimates of neither prevalence nor incidence were possible, the data compiled showed that the five neighborhoods with the highest rates were also the five neighborhoods with the highest proportion of non-Hispanic Black population.

Complete estimates of incidence were able to be determined for Boston as a whole for all new cases diagnosed between October 1, 2003 and September 30, 2004 because all hospital in- and out-patient records of new cases were able to be identified and reviewed during this period. The average annual estimate was found to be 6.3 per 100,000. Precise incidence estimates from the scientific literature on what other geographic areas of the U.S. have experienced do not exist, but estimates range from 3.5 – 10.5 per 100,000, depending upon the racial distribution of the population. The incidence among Caucasian populations has been found to be about 3.5 – 3.9 per 100,000 and 9.2 – 10.5 among African American or African Caribbean populations (Hochberg 1985, McCarty 1995). The Boston incidence estimate appears to be within the range observed for other populations.

Incidence was also estimated by neighborhood and for Boston covering a longer time period, January 1, 1999-September 30, 2004. These estimates are likely underestimates of the true incidence since they only included new cases diagnosed during this period who also had an in- or out-patient hospital visit between October 2003 and September 2004. Some new cases diagnosed since 1999 would have been excluded from the incidence estimates if they did not have a hospital visit during the 2003-2004 period. Nevertheless, these results found that certain neighborhoods had a higher incidence rate of lupus than others, although Roxbury was the only neighborhood with a statistically significantly higher rate than expected based on overall Boston rates. The Roxbury rates also appear to be slightly greater than reported for similar populations in the scientific literature.

To further characterize incidence in Boston neighborhoods, exploratory statistical analyses were conducted to evaluate any possible relationship with hazardous waste sites. The analyses were exploratory because they could only include cases diagnosed from 1999 and later. As mentioned above, this excludes a large proportion of cases. The analyses are also considered exploratory because it is not possible to know from existing data whether individuals could be exposed to any chemicals detected at a hazardous waste site or if the chemical contamination occurred prior to the diagnosis of lupus since these are cross-sectional analyses. The various reporting fields in the 21e database provide comprehensive information about individual waste spills, but these data are primarily for compliance purposes. In general, acute risks to human health are considered in assigning categories to 21e sites, but the categories are nonspecific particularly for chronic exposure scenarios. For example, a release may be categorized as a '2-Hour' site (the time frame in which the incident must be reported to MDEP) because of its potential impact on the local environment, but the release may pose little or no threat of human exposure to contaminants. Conversely, a relatively small amount of a contaminant might have potential impacts to human health if the opportunity exists for long-term chronic exposure but in the short term may be considered environmentally benign.

The analyses relating the incidence of lupus with the density of 21e sites as a whole found no relationship between higher lupus incidence and higher density of all 21e sites combined. Findings, however, were suggestive of a possible relationship with higher density of total tier classified 21e sites and tier classified sites with chemicals suspected of being associated with SLE, as well as sites with gasoline contaminants. It is probably important to note that many of these sites are related to former gasoline stations, so it is not clear whether the suggested association is due to proximity to the 21e site itself or fugitive emissions related to the operations of these facilities previously.

These analyses suggest that historical opportunities for exposure to industrial operations, rather than to the waste sites themselves, could have played some role in the patterns of lupus observed in Boston neighborhoods. However, the neighborhoods with a higher occurrence of lupus also have a larger proportion of higher risk individuals (e.g., minority populations), therefore the possible relationship between lupus and hazardous waste sites warrants further research.

Although these findings can only be considered exploratory for the reasons discussed above, a recent publication of similar work independently conducted in the Roxbury, Mattapan, North Dorchester neighborhoods by researchers at the Brigham and Women's hospital in Boston (in collaboration with the MDPH) found that living near some types of hazardous waste sites may have resulted in an earlier age of diagnosis for individuals with a particular genotype for glutathione-S-transferase (GST) genes (*Karlson et al, 2006*). Although this study does not conclude that living near hazardous waste sites might cause lupus, it suggests that the role of living near hazardous waste sites (or areas where exposure opportunities to gasoline constituents may have been higher in the past) should be studied further to determine the potential for gene-environment interaction for some individuals diagnosed with lupus. This may be important given that this genotype has also been suggested to act as an accelerant to developing lung cancer among those that smoke.

For analyses of linkage and incidence/prevalence estimation, there were a number of limitations or problems encountered that at a minimum affect the long-term feasibility of conducting lupus surveillance using the methods employed. One problem is in the variability in diagnosis. ACR classification criteria were initially thought to be useful for standardizing the definition of SLE vs. other related autoimmune diseases, but these criteria were established for assigning cases to clinical trials not for standardizing clinical diagnosis. The literature demonstrates that rheumatologists find some patients that meet 4 ACR criteria do not have SLE. Rheumatologists are reported to disagree with the diagnosis based on ACR classification criteria at a rate of 1 in 5 individuals (or up to 20%).

The original protocol for this surveillance effort called for the abstraction of ACR criteria for each patient by a board certified/eligible rheumatologist. Cases were to be defined by the presence of specified numbers of the 11 ACR criteria, and date of diagnosis was to be determined by the dates the ACR criteria were met. The expense and lack of availability of rheumatologists to perform the time consuming task of identifying the earliest dates for fulfilled ACR criteria from lengthy, sometimes poorly accessible medical records made this original protocol infeasible. The change in level of expertise to nurse abstractors resulted in a change in the definition of cases, since our scientific advisory committee indicated that the sometimes subjective ACR criteria could only be reliably abstracted by rheumatologists. Resource limitations together with the anticipated volume of 1,400 patients needing record review resulted in restricting abstraction so that only recent cases of SLE (defined as those whose earliest SLE diagnosis was in 1999 or later) would have more detailed information abstracted for case definition and geocoding.

The modified methodology also resulted in a number of challenges. Most diagnostic workups for SLE were done on an outpatient basis rather than during hospitalizations. There was variation among hospitals with regard to the location of clinic medical records and location of access to these for MDPH abstracting. Occasionally records in the database were entirely unavailable through hospital administrative procedures because they were part of a private practice. A number of patients did not have diagnostic workups or more detailed historical diagnostic information readily available because their visits were in service departments other than rheumatology, and they were seen elsewhere for SLE diagnosis and follow-up.

Reviewing records was extraordinarily labor intensive, particularly looking for diagnoses retrospectively in relation to time, i.e., “earliest” diagnosis, or “date” of diagnosis. Finding the date of earliest diagnosis was not only resource intensive, but seemed inconsistent in availability and reliability. First, diagnoses of possible SLE often were made by primary care physicians outside of the institutions, and the dates may not have been apparent in the abstracted medical record. Limiting dates to those 1999 or later did not save as much time as anticipated, since searches had to be made in records that were often not easily accessible. In addition, word choices found in the record were not always clear in terms of our categorizations. Since SLE is a disease that is a chronic multi-systemic disease that is often difficult to diagnose, sometimes the certainty expressed for the SLE diagnosis varied even for the same rheumatologist. Therefore, distinctions between definite and probable, and between probable and possible SLE were not always well delineated in the verbiage used in the medical records. Occasionally there was a difference in opinion between rheumatologists in the record. Sometimes a rheumatologist did not use SLE by name or abbreviation, although the patient seemed to be under consideration as having possible SLE.

The largest obstacle to reporting seemed to be the requirement to determine the date of diagnosis and other diagnostic details retrospectively, particularly at large institutions where individual physicians had large lupus practices. There were also rheumatologists who felt they did not have access to the billing databases, either due to the size of their institutions, or because they or their personnel were not familiar enough with the systems to query these databases.

CONCLUSIONS

Retrospective Surveillance of SLE in Boston required 927 records to be abstracted in order to identify an estimated 425 SLE cases with a definite or probable diagnosis of SLE even though all cases had been identified as lupus cases by hospital coding procedures. Therefore, more than twice the number of medical records needed to be reviewed to estimate the prevalence of actual cases of definite or probable SLE.

The prevalence of definite and probable SLE in Boston for all residents was found to be approximately 80.3 per 100,000 population. This prevalence estimate is within the range of prevalence estimates reported for the US population in the scientific literature. The prevalence among females was found to be about 9 times that in males. This finding was also consistent with the scientific literature. The average annual incidence appears to be highest in Roxbury, which was statistically significantly higher than expected based on Boston rates as a whole and could be in part due to the higher percentage of African-Americans residing in Roxbury compared with Boston.

Exploratory analyses conducted to investigate the possible relationship of lupus incidence with hazardous waste sites found that there was no relationship between higher lupus incidence and density of all 21e hazardous waste sites. However, a statistically significant finding of higher lupus incidence associated with neighborhoods with a higher density of tier classified hazardous waste sites (with chemicals suspected with being associated with SLE) suggested that further evaluation of the potential relationship between lupus and possible exposures from certain types of hazardous waste sites should be considered. This is largely due to the fact that it remains unclear whether the relationship between lupus and these sites is due to actual site release or potential opportunities for exposure during the period when industrial activities were actually operating or some other combination of factors.

RECOMMENDATIONS

- Increase community awareness:
    - Summarize study results for popular use
    - Hold community education forums with Women of Courage and other community-based coalitions
    - Train community members to do health education on SLE and provide stipends for them to do outreach and education
- Hold meetings with Boston officials to discuss broader policy implications
- Partner with community health centers and hospitals
    - Work with Massachusetts League of Community Health Centers to provide clinical training to providers
    - Circulate SLE screening tool and other reporting tools

- If adequate funding becomes available, future surveillance of SLE should focus on prospective case finding (i.e., as patients are diagnosed) and include case ascertainment from NHCs and private practice rheumatologists rather than hospitals alone.

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Figure 1: 21e Site Data for Pre-1999 Sites

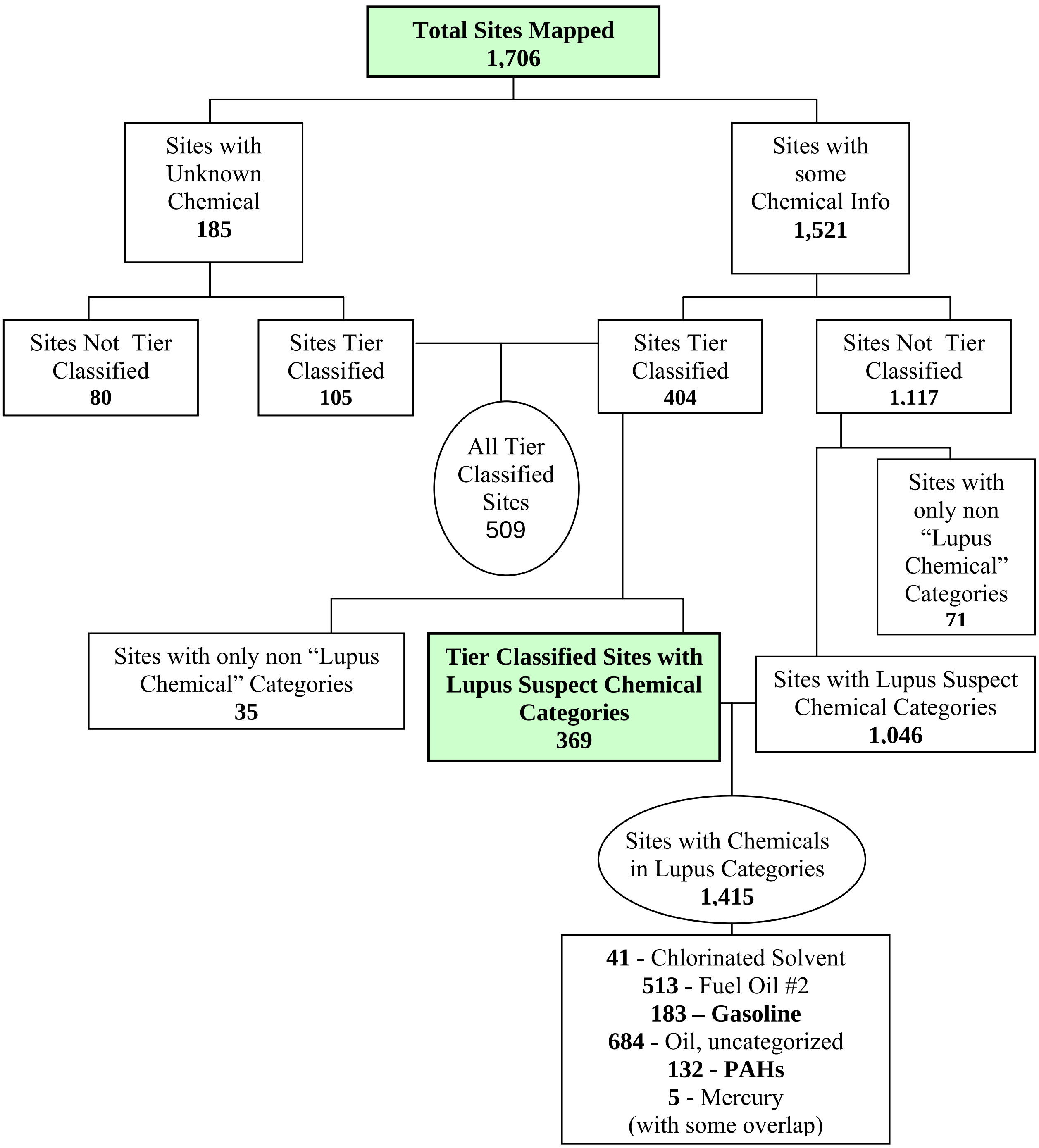

Figure 2: Density of All 21e Sites

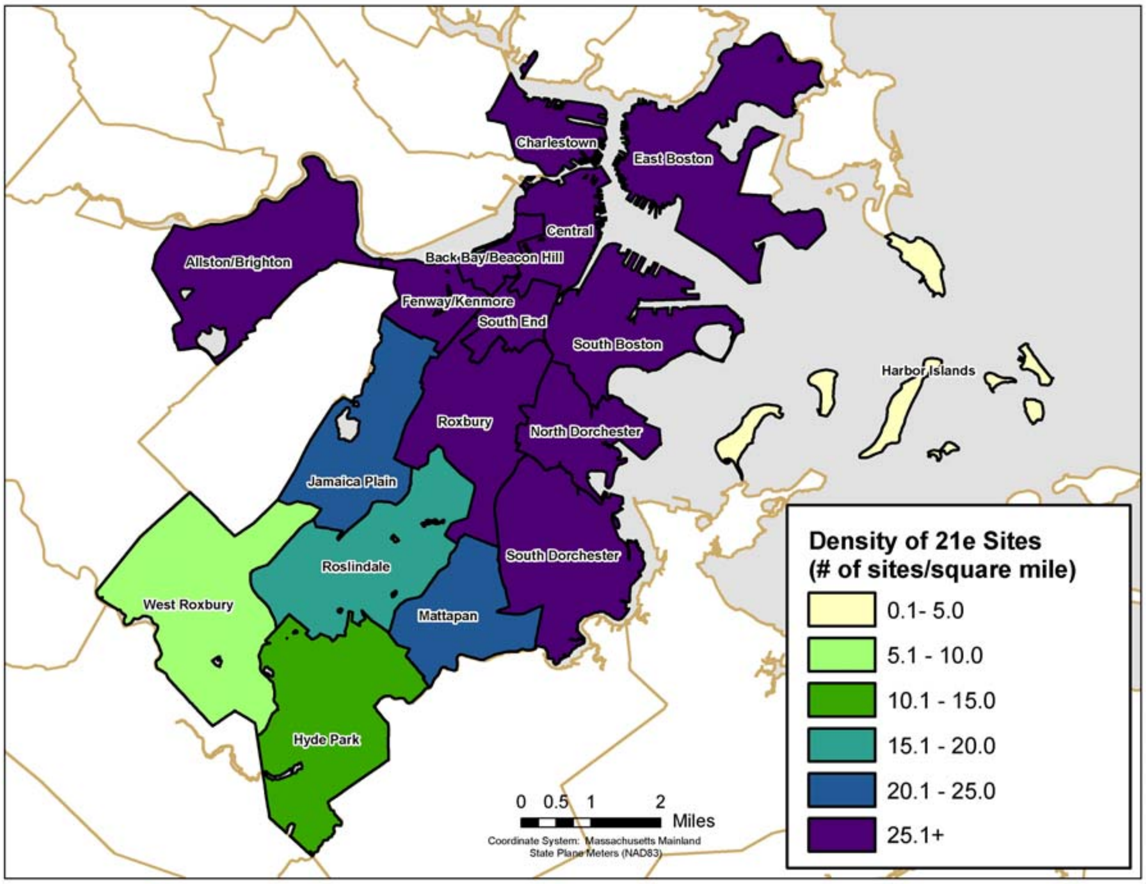

Figure 3: Density of Tier Classified 21e Sites with Lupus-Suspected Chemicals

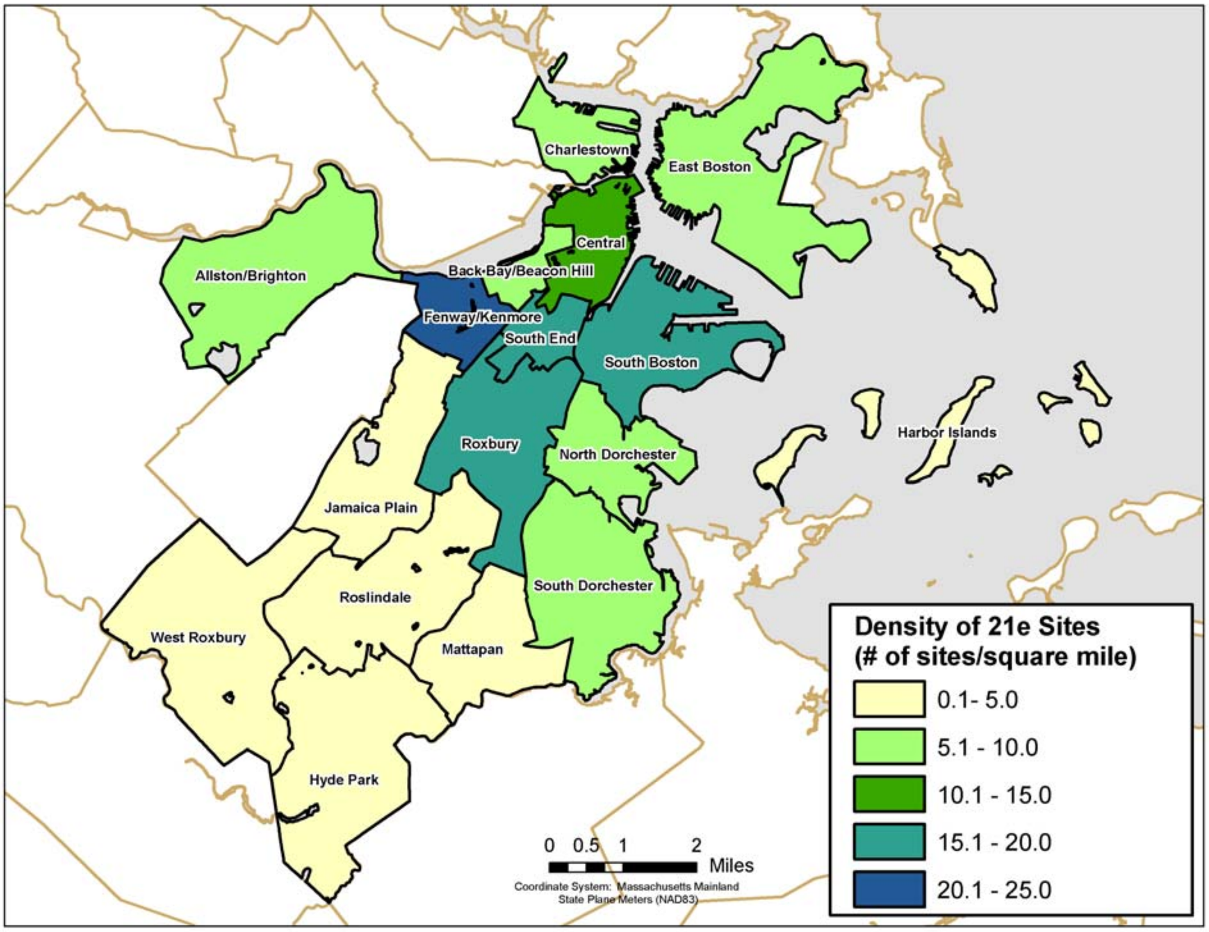

Figure 4: Boston Lupus Tracking Project Eligibility Flowchart

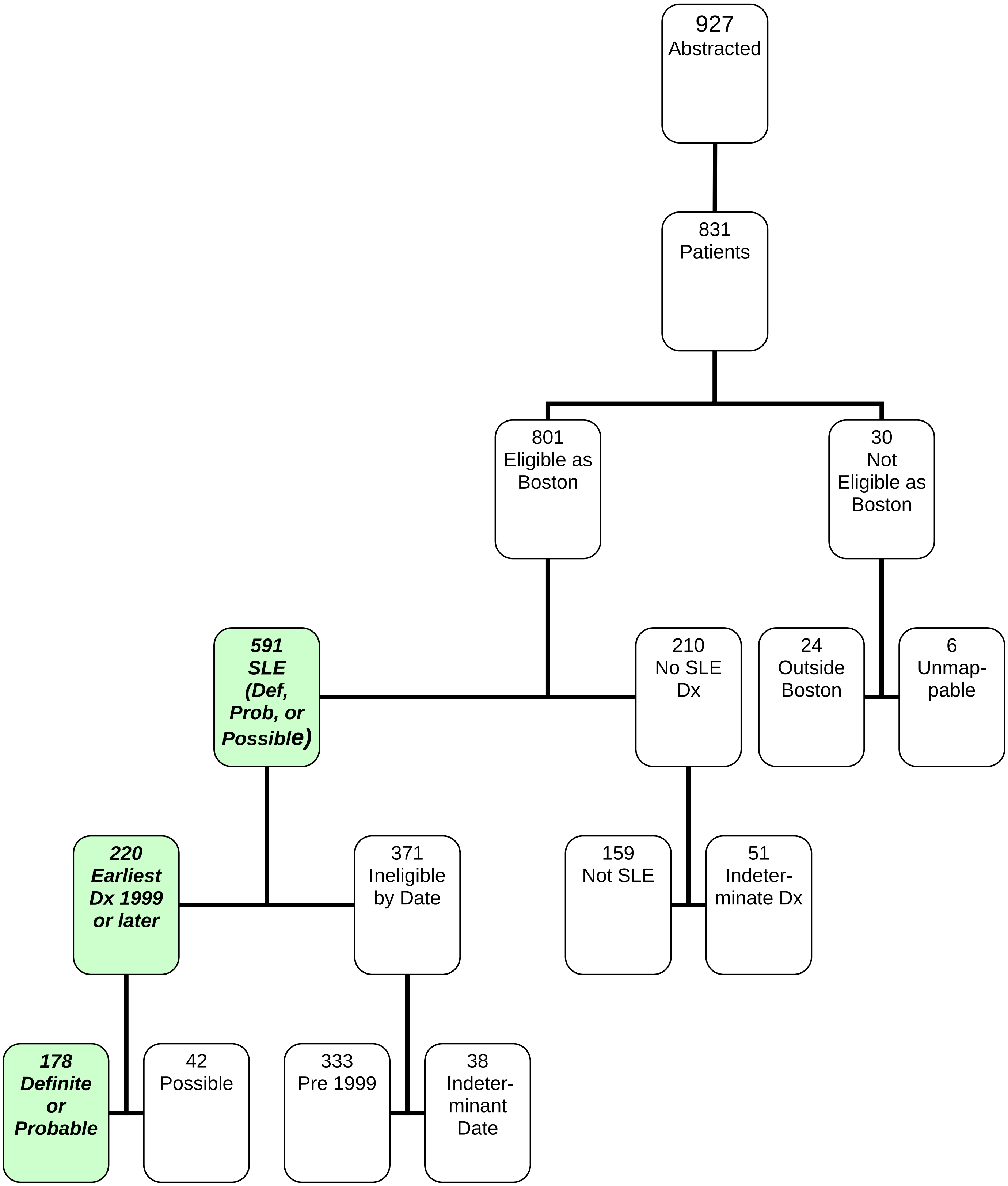

Figure 5: Comparison of Age Distributions Among Three Definitions of SLE Cases

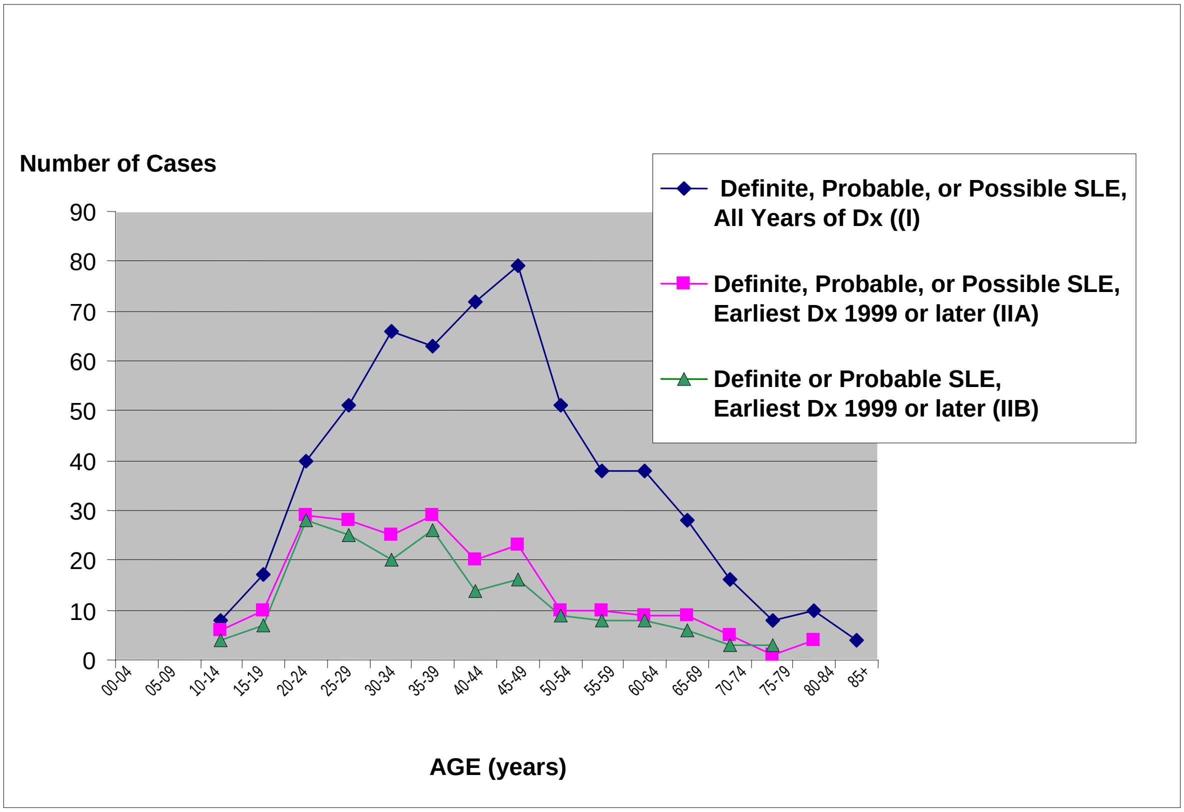

Figure 6: Individuals Identified By Hospitals and/or Neighborhood Health Centers with SLE and LE Coded Encounters (ICD9 710.0 and 695.4)

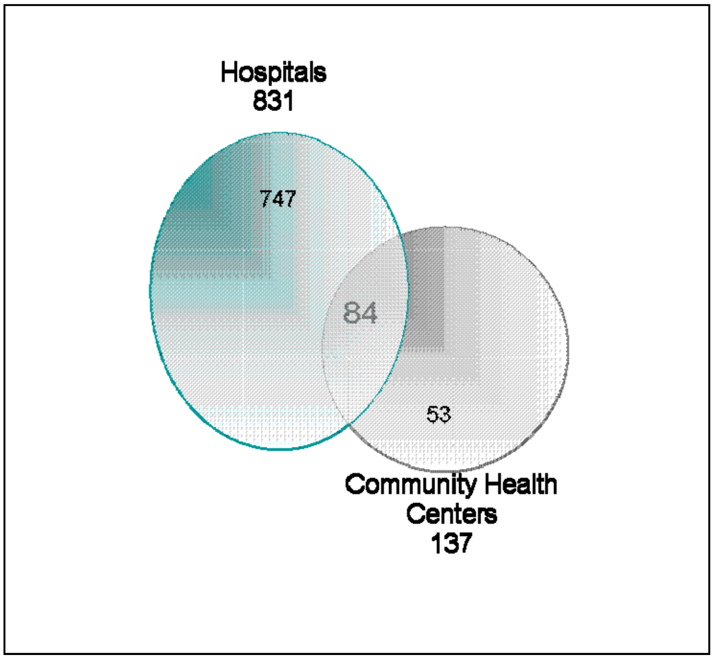

Figure 7: Density of Tier-Classified 21e Sites with Lupus-Suspected Chemicals and Neighborhoods with the Highest Rates of Lupus

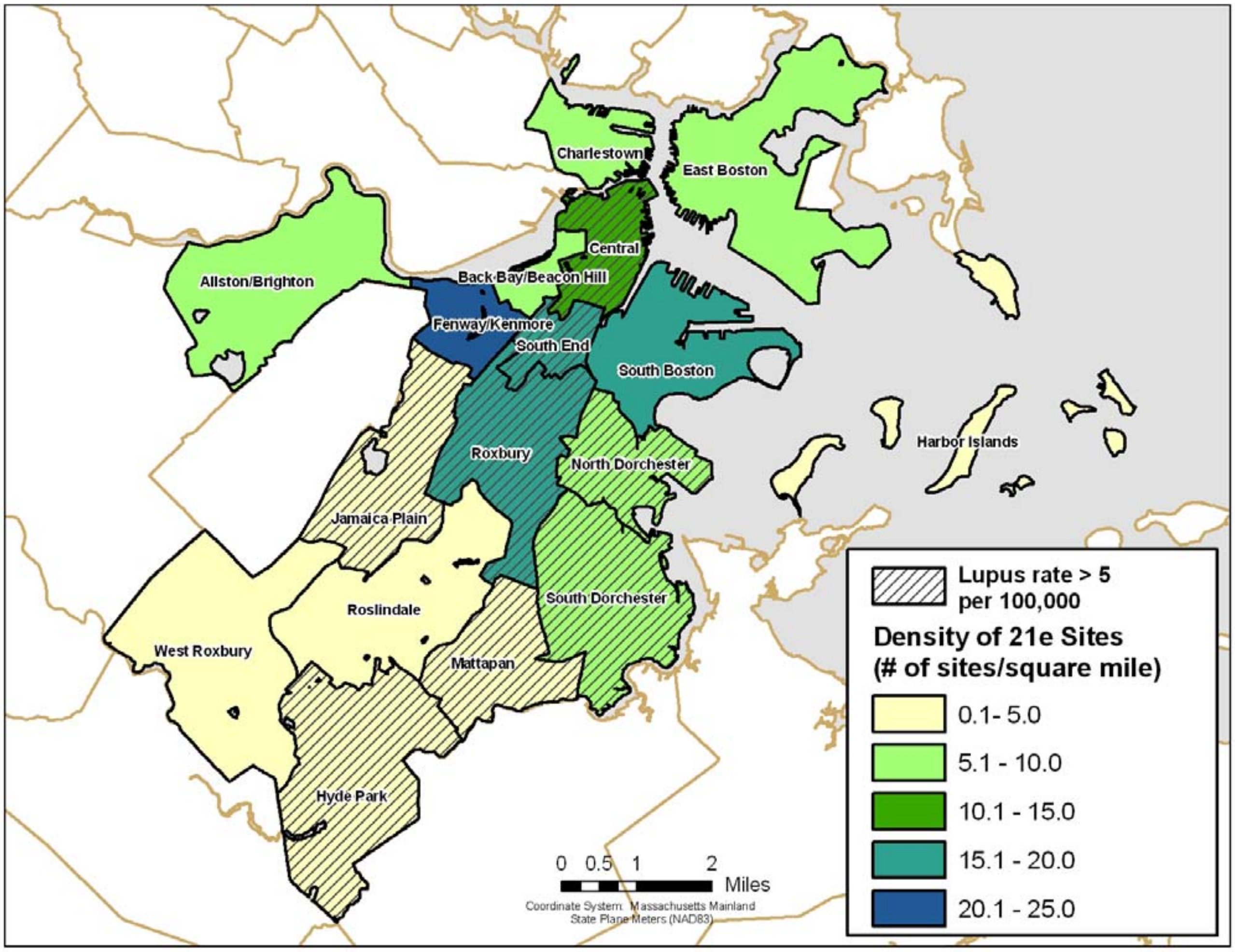

Table 1: Number of SLE Cases by Definition and Gender

	Cases: All Dates of Diagnosis	Cases: Recent Diagnosis*	
	Definite, Probable or Possible	Definite, Probable or Possible	Definite or Probable Only
Male	45	23	17
Female	546	197	161
Total	591	220	178
Male/Female Ratio	12:1	8:6	9:1

* Recent Dx = Earliest diagnosis of definite, probable, or possible SLE in 1999 or later

Table 2: Prevalence of SLE in Boston October 2003 - September 2004

		Cases: All Dates of Diagnosis		Estimated Cases: All Dates of Diagnosis*	
		Definite, Probable or Possible		Definite and Probable	
Race	Population	Cases	Cases per 100,000 Population	Cases	Cases per 100,000 Population
All races	589,141	591	100.3	425	80.3

* Estimated cases of definite and probable diagnoses for all dates of diagnosis from cases diagnosed in 1999 or later

Table 3: Prevalence of Cases Possible Stratified by Gender Among "All Races" for All Years of Diagnosis

All Races	Cases	Population	Observed Prevalence of Definite, Probable, and Possible Cases (cases/100,000)	Estimated Prevalence of Definite and Probable Cases (cases/100,000)*
Male	45	283,588	15.9	12.7
Female	546	305,553	178.7	143.0
M & F	591	589,141	100.3	80.3

*"80%" is the prevalence we estimate we might have found if only definite and probable cases were counted. This percentage was extrapolated from the percent of recent cases that were found to be definite or probable.

Table 4: Incidence* of New SLE Diagnoses in Boston, October 2003 to September 2004

		(A) Definite, Probable or Possible		(B) Definite or Probable Only	
	Population	Cases	Cases per 100,000	Cases	Cases per 100,000
All Races	589,141	57	9.7	37	6.3

*Incidence of earliest diagnosis of definite, probable or possible SLE

Table 5: Average Annual SLE Incidence Rates of Cases in Boston and Boston Neighborhoods with a Definite or Probable SLE Diagnosis, 1999-2004

Neighborhood	Cases - All Races*	Total Population	Cases per 100,000
Allston/Brighton	10	69,648	2.4
Back Bay/Beacon Hill	3	21,412	2.3
Central	**9**	**28,911**	**5.2**
Charlestown	3	15,195	3.3
East Boston	9	38,413	3.9
Fenway/Kenmore	6	38,765	3.9
Harbor Islands	0	640	0.0
Hyde Park	**16**	**34,420**	**7.8**
Jamaica Plain	**12**	**38,124**	**5.2**
Mattapan	**17**	**35,728**	**7.9**
North Dorchester	**9**	**28,668**	**5.2**
Roslindale	5	32,402	2.6
Roxbury	**37**	**59,392**	**10.4****
South Boston	**6**	**29,938**	**3.3**
South Dorchester	**20**	**62,269**	**5.4**
South End	**12**	**26,463**	**7.6**
West Roxbury	4	28,753	2.3
Boston*	178	589,141	5.0

Numbers in Bold represent Neighborhood/Race categories where there were more than 4 cases and the prevalence was greater than Boston for that race
Boston t

* Boston total does not equal the sum of neighborhoods due to unknown residence of cases.
** Statistically significantly greater than Boston.

Table 6: October 2003 – November 2004 SLE Standardized Incidence Ratios (SIR) Boston Neighborhoods with Greater Than 4 Cases (Definite and Probable Diagnoses in 1999 or Later, All Races)

Neighborhood	Observed	Expected	SPR	Lower CI	Upper CI
Roxbury	37	17.0	217.5*	153.1	299.8
Mattapan	17	10.7	159.3	92.8	255.1
South End	12	7.6	158.4	81.8	276.8
Hyde Park	16	10.1	158.1	90.3	256.7
South Dorchester	20	18.0	111.4	68.0	172.1
North Dorchester	9	8.2	109.3	49.9	207.4
Central	9	8.9	101.5	46.3	192.6
Jamaica Plain	12	12.2	98.5	50.8	172.0
East Boston	9	10.5	85.6	39.1	162.5
South Boston	6	9.5	63.5	23.2	138.1
Roslindale	5	9.7	51.8	16.7	120.8
Fenway/Kenmore	6	11.9	50.2	18.3	109.4
Allston/Brighton	10	22.7	44.0*	21.1	80.9

* statistically significant ($p < 0.05$)

Table 7: Density* of Pre-1999 21e Sites by Contamination Classification

Neighborhood	Any 21e	Tier Classified	Tier Class / Lupus Suspect Chem	PAH	Gasoline
Allston/Brighton	51	9	12	5	6
Back Bay/Beacon Hill	57	10	13	5	3
Central	79	14	21	7	6
Charlestown	56	10	16	8	3
East Boston	28	7	9	3	2
Fenway/Kenmore	81	21	30	10	9
Harbor Islands	3	1	1	0	0
Hyde Park	14	2	3	1	1
Jamaica Plain	23	4	5	2	1
Mattapan	214	3	6	4	2
North Dorchester	35	8	10	4	5
Roslindale	15	3	6	2	3
Roxbury	62	15	22	7	10
South Boston	72	15	21	6	5
South Dorchester	29	8	9	3	5
South End	96	19	29	10	5
West Roxbury	9	3	4	2	2

*Number of 21e sites/square mile

Table 8a-e: Comparison of SLE Incidence Between Neighborhoods of Higher and Lower 21e Site Densities[t]

Table 8a: All Mapped 21e Sites Combined (1,706 sites)

Neighborhood Site Density	Cases	Population	Average Annual Incidence[tt]
Higher*	86	289,724	5.0
Lower**	92	299,417	5.1

* >= 51 sites/square mile

** < 51 sites/square mile

Odds Ratio 0.97

Chi square 0.05

P = 0.82

Table 8b: Tier Classified Hazardous Waste Sites (509 sites)

Neighborhood Site Density	Cases	Population	Average Annual Incidence[tt]
Higher*	70	183,469	6.4
Lower**	108	405,672	4.4

* >= 14 sites/square mile

** < 14 sites/square mile

Odds Ratio 1.43

Chi square 5.56

p < 0.02

[t] Cut-off for "Higher" and "Lower" designation was the midpoint of the range in density (among the 17 Boston Neighborhoods) for each specific classification of pre-1999 hazardous waste site

[tt] Definite and Probable SLE Cases/100,000 who were diagnosed since 1999 and who visted a hospital between October 1, 2003 - September 30, 2004

Table 8c: Tier Classified Hazardous Waste Sites with Lupus-Suspect Contaminants (369 sites)

Neighborhood Site Density	Cases	Population	Average Annual Incidence[tt]
Higher*	70	183,469	6.4
Lower**	108	405,672	4.4

* >= 14 sites/square mile

** < 14 sites/square mile

Odds Ratio 1.43

Chi square 5.56

$p < 0.02$

Table 8d: Hazardous Waste Sites with Gasoline Contaminants (183 sites)

Neighborhood Site Density	Cases	Population	Average Annual Incidence[tt]
Higher*	43	98,157	7.3
Lower**	135	490,984	4.6

* >= 6 sites/square mile

** < 6 sites/square mile

Odds Ratio 1.59

Chi square 7.20

$p<0.01$

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[t] Cut-off for "Higher" and "Lower" designation was the midpoint of the range in density (among the 17 Boston Neighborhoods) for each specific classification of pre-1999 hazardous waste site

[tt] Definite and Probable SLE Cases/100,000 who were diagnosed since 1999 and who visited a hospital between October 1, 2003 - September 30, 2004

Table 8e: Hazardous Waste Sites with PAH Contaminants (132 sites)

Neighborhood Site Density	Cases	Population	Average Annual Incidence[tt]
Higher*	73	198,664	7.3
Lower**	105	390,477	4.6

* >= 6 sites/square mile

** < 6 sites/square mile

Odds Ratio 1.37

Chi square 4.23

$p < 0.04$

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[t] Cut-off for "Higher" and "Lower" designation was the midpoint of the range in density (among the 17 Boston Neighborhoods) for each specific classification of pre-1999 hazardous waste site

[tt] Definite and Probable SLE Cases/100,000 who were diagnosed since 1999 and who visited a hospital between October 1, 2003 - September 30, 2004